

REMARKS

Reconsideration of the present application is respectfully requested in view of the following remarks. Claims 43-50 are pending and under examination. Without acquiescence or prejudice, claims 43 and 49 are amended and new claim 51 is added to particularly point out and distinctly claim certain embodiments of Applicants' invention, and claim 50 is canceled. No new matter has been added by the amendments, support for which can be found in the as-filed specification, for example, at page 12, line 30 to page 13, line 4; page 20, line 1, to page 21, line 11; and pages 23-25.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, INDEFINITENESS

Claims 49 and 50 stand rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The Examiner alleges that certain conditions in claim 50 are not cancerous conditions, as required in claim 49.

Applicants thank the Examiner for noting this. Nonetheless, without acquiescence or prejudice, claim 50 has been canceled, rendering moot the rejection of that claim, and claim 49 no longer refers to cancer pain. Applicants therefore respectfully request withdrawal of this rejection.

REJECTIONS UNDER 35 U.S.C. § 103

A. Claims 43-45, 48, and 49 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* (*Regional Anesthesia and Pain Medicine*. 18:4, 1993) and Grond *et al.* (*Pain*. 79:15-20, 1999). Nickel *et al.* are alleged to teach the combination of flupirtine and morphine for treating cancer pain. It is then alleged that this combination would have been considered obvious for treating neuropathic cancer pain.

B. Claim 46 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Perovic *et al.* (*Neurodegeneration*. 4:369-374, 1995). Perovic *et al.* are alleged to teach that flupirtine is a clinically safe compound that is non-sedating in most cases, from which the Examiner alleges that it would have been obvious to use flupirtine in combination with negligible amounts of morphine to avoid overt sedation.

C. Claim 47 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Devulder *et al.* The Examiner relies on Nickel *et al.* and Grond *et al.* as above, and then alleges that Devulder *et al.* teach the recited dosages of flupirtine *alone* for treating neuropathic pain.

D. Claim 50 stands rejected under 35 U.S.C. § 103(a) for alleged obviousness over Nickel *et al.* and Grond *et al.*, further in view of Cleary (*Cancer Control*. 7:120-131, 2000). Cleary is alleged to teach that cancer pain has a neuropathic component, and further identifies certain of the specific cancers in claim 50.

Applicants respectfully traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness over the combination of cited references. Mainly, it is respectfully submitted that a *prima facie* case of obviousness has not been established for the use of flupirtine in combination with an opioid for treating neuropathic pain, including neuropathic cancer pain.

First, it is respectfully submitted that the Action appears to confuse the relationship not only between nociceptive pain and neuropathic pain, but also between cancer pain and neuropathic pain. For instance, it is emphasized that nociceptive pain and neuropathic pain are statistically similar in their *severity*, and that their treatment follows the same principles (*see, e.g.*, the Action, page 4, lines 16-17; and pages 4-5, carryover sentence). Applicants respectfully disagree, and submit, for example, that comparisons of *severity* are irrelevant. Instead, as previously discussed on the record, their different mechanisms of action are most relevant, and prevent nociceptive pain from being predictive of neuropathic pain.

The Action also appears to suggest that the cancer patients of Nickel *et al.* necessarily have neuropathic pain. For example, it is asserted that cancer pain is a model of neuropathic pain, and a major problem for cancer patients (*see, e.g.*, the Action, page 4, lines 7-8; and page 5, lines 16-17). It is then alleged that it would have been obvious to use the same treatment for neuropathic pain as for cancer pain. Applicants respectfully disagree. As previously discussed, the statistical relationship between cancer pain and neuropathic pain shows that only a relatively small percentage of cancer patients have neuropathic pain. Hence, even though it may be a major problem for those few cancer patients, within an entire population their

cancer pain does not provide a predictive model for neuropathic pain. Accordingly, the alleged treatment of cancer pain by Nickel *et al.* does not necessarily (*i.e.*, statistically) represent a predictive model of neuropathic pain.

The Action then argues against Applicants' data relating to (lack of) overt sedation, at least as that data contributes to the non-obviousness of the claims. Specifically, the Action appears to suggest Nickel *et al.* predict these effects by their reference to "behavior changes." As previously discussed, Applicants respectfully disagree, and submit that the skilled artisan would have recognized sedation as a "side-effect" not a "behavior," and thus would have understood the study of Nickel *et al.* to say nothing meaningful about sedation.

Nonetheless, without acquiescence or prejudice, and merely to expedite allowance of certain embodiments of Applicants' invention, the instant claims have been amended to exclude the treatment of cancer-related neuropathic pain. It is respectfully submitted that these amendments obviate the rejections set forth in sections A-D above.

Applicants therefore submit that the instant claims satisfy the requirements of non-obviousness over the combination of cited references, and respectfully request withdrawal of the rejections under 35 U.S.C. §103(a).

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,
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